PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 May 2000 (05.05.00)	
International application No. PCT/US99/19615	**Applicant's or agent's file reference** PB-0003 PCT
International filing date (day/month/year) 26 August 1999 (26.08.99)	**Priority date** (day/month/year) 01 September 1998 (01.09.98)
Applicant WALKER, Michael, G. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 March 2000 (27.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 9/64, C07K 14/47, C12N 15/57, 15/12, 5/10, A61K 38/48, 38/17, C07K 16/18, 16/40, C12Q 1/68

A2

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60/155,194	1 September 1998 (01.09.98)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application

US	60/155,194 (CIP)
Filed on	1 September 1998 (01.09.98)

(71) Applicant *(for all designated States except US)*: INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).

(72) Inventors; and

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(74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: GENES ASSOCIATED WITH NEUROTRANSMITTER PROCESSING

(57) Abstract

The invention provides five new genes associated with neurotransmitter processing and polypeptides encoded by those genes. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing diseases.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PB-0003 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 19615	26/08/1999	01/09/1998
Applicant		
INCYTE PHARMACEUTICALS, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readble form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/19615

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see additional sheet, subject 1.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

B x III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The invention provides five genes associated with neurotransmitter processing and polypeptides encoded by those genes. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing diseases.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1,2,3,5,6,7,10,11 (partially)

A polynucleotide comprising a gene that is co-expressed with one or more neurotransmitter-processing-specific genes in a plurality of biological samples, wherein each neurotransmitter-processing specific gene is selected from the group conisting of L-tyrosine hydroxylase (TH), aromatic amino acid decarboxylae (AADC), dopamine beta-hydroxylase (DBH), nicotinic acetylcholine receptor alpha3 subunit precursor(nAchR-alpha3), secretogranin I and II, Rab3a, human cocaine and amphetamine regulated transcript (hCART), vesicular monoamine transporter 1 (hVMAT) and ARIX homeodomain protein, comprising such polynucleotide the sequence of SEQ ID NO:1, expression vectors and host cells, pharmaceutical compositions containing the polynucleotide of SEQ ID NO:1 and methods for diagnosis, prevention and treatment of diseases associated with altered expression of SEQ ID NO:1.

2. Claims: 1,2,3,5,6,7,10,11 (partially)

As subject 1 but comprising the polynucleotide sequence of SEQ ID NO:2.

3. Claims: 1,2,3,5,6,7,10,11 (partially)

As subject 1 but comprising the polynucleotide sequence of SEQ ID NO:3.

4. Claims: 1,2,3,5,6,7,10,11 (partially) and 4,8,9 (complete)

As subject 1 but comprising the polynucleotide sequence of SEQ ID NO:4 and the polypeptide sequence encoded thereby (SEQ ID NO:6); pharmaceutical compostions containing the polypeptide of SEQ ID NO:6 and antibodies against said polypeptide.

5. Claims: 1,2,3,5,6,7,10,11 (partially)

As subject 1 but comprising the polynucleotide sequence of SEQ ID NO:5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/19615

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/64 C07K14/47 C12N15/57 C12N15/12 C12N5/10
A61K38/48 A61K38/17 C07K16/18 C07K16/40 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZELLMER E ET AL: "A homeodomain protein selectively expressed in noradrenergic tissue regulates transcription of neurotransmitter biosynthetic genes." JOURNAL OF NEUROSCIENCE, vol. 15, no. 12, December 1995 (1995-12), pages 8109-8120, XP000863055 cited in the application figure 2 page 8111 -page 8112 --- -/--	1,3

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2000	11 05 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALCONADA RODRIG.., A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMADA K ET AL: "Detection of tyrosine hydroxylase and phenylethanolamine-N-methyltransferase messenger RNAs in the mouse adrenal gland and the brain by in situ hybridization." HISTOCHEMISTRY, vol. 97, no. 3, 1992, pages 201-206, XP000863050 figures 1,2 page 202-204 ---	1,3
X	WESSEL T C ET AL: "Parallel upregulation of catecholamine-synthesizing enzymes in rat brain and adrenal gland: effects of reserpine and correlation with immediate early gene expression." BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH., vol. 15, no. 3,4, October 1991 (1991-10), pages 349-360, XP000863122 figure 1, pannels A,C,E figure 2, pannels A,C,E,G figure 4, pannels A,C page 353-354 ---	1,3
X	SCHALLING M ET AL: "Colocalization of neurotransmitters analyzed by in situ hybridization." EUROPEAN NEUROPSYCHOPHARMACOLOGY, vol. 1, no. 2, 1991, pages 173-176, XP000863049 figure 1 page 174 ---	1,3
X	NAGASE T ET AL: "Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro." DNA RESEARCH, vol. 5, no. 1, 28 February 1998 (1998-02-28), pages 31-39, XP002103187	1-3,5-7
A	table 2 -& DATABASE GENEMBL [Online] 10 April 1998 (1998-04-10) OHARA,O., NAGASE,T. AND ISHIKAWA,K.: "Homo sapiens mRNA for KIAA0604 protein, complete cds." XP002127316 Accession number AB011176 --- -/--	10,11

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMOTO N ET AL: "Endothelin-converting enzyme-2 is a membrane-bound, phosphoramidon- sensitive metalloprotease with acidic pH optimum." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 25, 25 June 1995 (1995-06-25), pages 15262-15268, XP002125420	1-3,5-7
A	figure 1 -& DATABASE GENEMBL [Online] 15 July 1995 (1995-07-15) YANAGISAWA,M.: "Bos taurus endothelin converting enzyme-2 (ECE-2) mRNA, complete cds" XP002127317 Accession number U27341	10,11

09/786,136

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PB-0003 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/19615	26 August 1999 (26.08.1999)	01 September 1998 (01.09.1998)

International Patent Classification (IPC) or national classification and IPC

IPC(7): C12N 9/64, 5/10, 15/12, 15/57; C12Q 1/68; C07K 14/47, 16/18, 16/40; A61K 38/17, 38/48 and US Cl.: 536/23.2, 23.5, 435/6, 69.1, 226, 252.3, 320.1; 530/387.1; 514/2

Applicant

INCYTE PHARMACEUTICALS, INC.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 March 2000 (27.03.2000)	18 September 2000 (18.09.2000)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer William Moore Telephone No. (703)308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/19615

I. Basis f the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-27 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 28 and 29, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-5, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/19615

V. Reasoned statement under Article 35(2) with regard t novelty, inventive step r industrial applicability; citations and explanati ns supporting such statement

1. STATEMENT

Novelty (N)	Claims	10 and 11	YES
	Claims	1-3 and 5-7	NO
Inventive Step (IS)	Claims	10 and 11	YES
	Claims	1-3 and 5-7	NO
Industrial Applicability (IA)	Claims	1-3,5-7,10 and 11	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by Schalling et al., European Neuropsychopharmacology, 1991, Vol. 1, pages 173-176, who disclose, Figure 1, the coexpression of a gene encoding phenylethanolamine N-methyltransferase [PNMT] with the tyrosine hydroxylase [TH] gene recited in claim 1. Since a PNMT-encoding cDNA had previously been isolated in order to prepare the hybridization probe used by Schalling et al., their disclosure of PNMT gene coexpression inherently anticipates the subject matter of claim 1.

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by Wessel et al., Molecular Brain Research, October 1992, Vol. 15, pages 349-360, who disclose, Figure 2, the coexpression of a gene encoding phenylethanolamine N-methyltransferase [PNMT] with the tyrosine hydroxylase [TH] and dopamine-beta-hydroxylase [DBH] genes recited in claim 1. Since a PNMT-encoding cDNA had previously been isolated in order to prepare the hybridization probe used by Wessel et al., their disclosure of PNMT gene coexpression inherently anticipates the subject matter of claim 1.

Claims 1 and 3 lack novelty under PCT Article 33(2) as being anticipated by Yamada et al., Histochemistry, 1992, Vol. 97, pages 201-206, who disclose, Figure 1, the coexpression of the gene encoding phenylethanolamine N-methyltransferase [PNMT] with the tyrosine hydroxylase [TH] gene recited in claim 1 as well as the presence of both the coexpressed PNMT and TH polypeptide products by immunohistochemical procedures, Figure 2. Since a PNMT-encoding cDNA had previously been isolated in order to prepare the hybridization probe used by Yamada et al., and since a PNMT polypeptide had previously been isolated to prepare the anti-PNMT antiserum of Yamada et al., their dual disclosures of PNMT gene coexpression inherently anticipate the subject matters of claims 1 and 3.

Claims 1 and 3 lack novelty under PCT Article 33(2) as being anticipated by Zellmer et al., The Journal of Neuroscience, December 1995, Vol. 15, pages 8109-8120, who disclose, Figure 1 and discussion at pages 8111-8115, the isloation of a polynucleotide transcript of the gene encoding the homeobox protein Arix with the dopamine-beta-hydroxylase [DBH] gene anticipating the subject matter of claim 1, which does not exclude coexpression of its enumerated genes. Zellmer also disclose the encoded amino acid sequence of the Arix transcript, inherently anticipating the subject matter of claim 3.

Claims 1-3 and 5-7 lack novelty under PCT Article 33(2) as being anticipated by Emoto et al., The Journal of Biological Chemistry, June 1995, Vol. 270, pages 15262-15266, who disclose, Figure 1, the isolation of a polynucleotide transcript of a gene encoding a bovine endothelin-converting enzyme-2 [bECE-2], which transcript comprises the nucleic acid sequence of SEQ ID NO:1 herein, adding 5'-coding sequences further to those present in SEQ ID NO:1 herein, meeting limitations of claims 1 and 2, Emoto et al. also disclosed the encoded ECE-2 amino acid sequence, the cloning of the transcript in the eukaryotic expression vector pME18Sf, the recombinant expression of the [ECE-2] gene product in transformed CH)-K1 cells, and the isolation of the product for activity assays, Figures 4 and 5, anticipating the subject matters of claims 3, 5 and 6, and its formulation in a composition for cleaving

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

endothelin substrate, inherently anticipating the subject matter of claim 7.

Claims 1 and 2 lack novelty under PCT Article 33(2) as being anticipated by Nagase et al., DNA Research, February 1998, Vol. 5, pages 31-39, who disclose, Figure 1 and Tables 1 and 2, the isolation of a 3.2kb polynucleotide transcript, termed KIAA0604 of a gene capable of hybridizing to SEQ ID NO:1 herein encoding a human endothelin-converting enzyme-2 analog [hECE-2], adding 5'-coding sequences further to those present in SEQ ID NO:1 herein. The nucleic acid sequence and the encoded sequence of 765 amino acids were made public of 10 April 1998 in the NCBI nucleotide sequence database under the accession number ABO11176 meeting limitations of claims 1-3. Emoto et al. also disclosed the encoded ECE-2 amino acid sequence, the cloning of the transcript in the eukaryotic expression vector pME18Sf, the recombinant expression of the [ECE-2] gene product in transformed CH)-K1 cells, and the isolation of the product for activity assays, Figures 4 and 5, anticipating the subject matters of claims 3, 5 and 6, and its formulation in a composition for cleaving endothelin substrate, inherently anticipating the subject matter of claim 7.

Claims 3 and 5-7 lack an inventive step under PCT Article 33(3) as being obvious over Nagase et al., DNA Research, February 1998, Vol. 5, pages 31-39, in view of Emoto et al., discussed above. It would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the hECE-2 coding sequence disclosed by Nagase et al. in the place of the bECE-2 coding sequence in the expression vecor of Emoto et al. and to transform the CHO-K1 host cells of Emoto et al. in order to recombinantly express the hECE-2 gene product in order to isolate the clinically-important human product for activity assays, meeting limitations of claims the subject matters of claims 3, 5 and 6, and further obvious to such an artisan at that time to formulate a composition comprising the hECE-2 for cleaving a human endothelin substrate, meeting limitations of claim 7.

Claims 10 and 11 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest that the bECE-2 or the hECE-t cDNA transcripts, or portions thereof, should be used in a diagnostic method for detecting altered gene expression of claim 10, nor does the prior art teach of fairly suggest how the metalloprotease products of the bECE-2 or hECE-2 transcripts might me used in a method for treating or preventing a disease associated with altered gene expression of claim 11.

---------- NEW CITATIONS ----------